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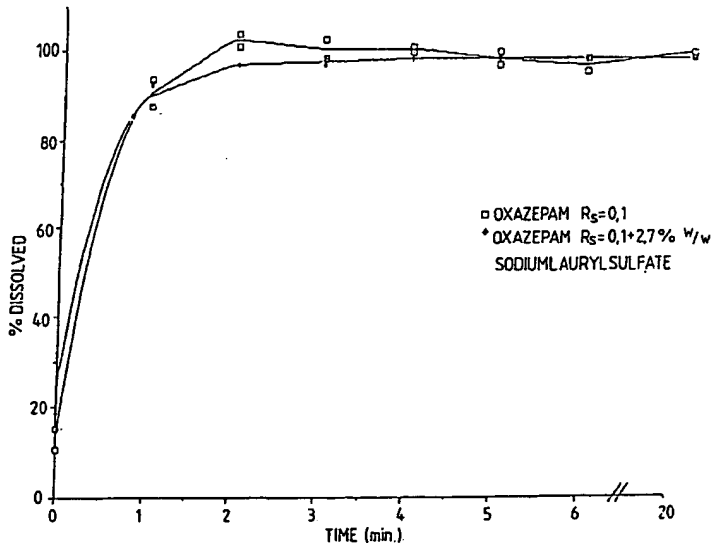

(57) Abstract

A pharmaceutical composition for rapid release of active pharmaceutical substance contains at least one finely-divided, hydrophobic pharmaceutical substance together with a water-soluble carrier. According to the invention, the composition also contains at least one surfactant in intimate mixture with the pharmaceutical substance.

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A pharmaceutical composition for rapid retease of the active component comprising an orderred mixture and a surfactant.

The present invention relates to a pharmaceutical composition which exhibits improved release of the pharmaceutical substance. More specifically, but not exclusively, the invention relates to a pharmaceutical composition which contains a considerable amount of active pharmaceutical substance but which, nevertheless, exhibits a high rate of pharmaceutical-substance release.

It is known to formulate pharmaceutical compositions as so-called ordered mixtures in which very fine particles of a hydrophobic pharmaceutical substance adhere to the surfaces of larger particles of a water-soluble carrier substance. The carrier particles dissolve in the presence of water and form a deposit, wherewith the adherent particles of pharmaceutical substance disperse throughout the liquid. This eliminates the inherent tendency of the particles of hydrophobic pharmaceutical substance to collect into not-readily dissolvable and dispersible aggregates.

The so-called surface-area ratio, R_s,constitutes a measurement of the quantity of particulate therapeutically active agent which will adhere to the surfaces of the larger carrier particles. R_s is defined as the ratio of the projected surface of the adherent particles to the total external surface-area of the carrier particles. A more detailed description of how this surface-area ratio is determined is given by C. Nyström, J. Mazur and J. Sjögren in International Journal of Pharmaceutics, 10: pages 209-218 (1982).

It is found that with increasing values of the surface-area ratio R_s, the solubility properties of the substance will be impaired to a commensurate degree and that the ordered mixture no longer provides an improvement. This is due to the fact that because of their hydrophobic properties, the particles of pharmaceutical substance prevent the penetration of water to the underlying carrier particles, despite the fact that the adherent particles do not cover the whole of the surface of the carrier particles.

Endeavours have been made to improve the dissolution rate of such compositions by incorporating a pharmaceutical disintegrant or "explosive" substance of known kind. This has provided some improvement, since the carrier particles the decompose more readily and since the formation of agglomerates from the particulate hydrophobic pharmaceutical substance is prevented. Good results are obtained at surface-area ratios of up to about 0.5, but at ratios above this value the dissolution rate again falls significantly. As in the case of compositions which lack the inclusion of a disintegrant, this fall in the dissolution rate is due to the fact that the fine particles of pharmaceutical substance form a dense network which cannot be penetrated by the water, because of the hydrophobic properties of the particles. The carrier particle with particles of pharmaceutical substance adhering thereto thus behaves as a large aggregate of solely pharmaceutical-substance particles.

It is evident that an improvement is highly desirable which will enable higher surface-area ratios to be achieved when mutually combining carrier particles and particles of pharmaceutical substance while maintaining

good dissolution properties. Such an improvement would enable a pharmaceutical dosage unit, e.g. a tablet, to contain a large quantity of pharmaceutical substance without impairing its solubility rate.

Another method of obtaining a composition comprising a finely-divided pharmaceutical substance in combination with a water-soluble carrier is to precipitate the pharmaceutical substance in a fine particulate form from a solution of said substance in the carrier. For instance, the pharmaceutical substance can be soluble in the carrier at high temperature, but not-readily dissolved at room temperature, wherein a fine dispersion of the pharmaceutical substance is obtained in the carrier, by cooling the solution therein to room temperature under controlled conditions. This will result in a fine dispersion of the hydrophobic pharmaceutical substance in the water-soluble carrier in which the particles of pharmaceutical substance are mutually separated. Consequently, the formation of not-readily dissolved aggregates is prevented, when the composition is dissolved in water.

In this case, the carrier may consist of polyethylene glycol, which is able to dissolve many hydrophobic pharmaceutical substances in heat, these substances subsequently precipitating in a finely dispersed form when the carrier cools. The polyethylene glycol may be more or less highly viscous or preferably solid, at room temperature, depending on the degree of polymerisation.

However, it is found that the rate of dissolution decreases markedly when the proportion of pharmaceutical substance in such a dispersion exceeds a given value, so that the composition becomes less useful for the purpose

intended. This is due to the fact that with increasing proportions of pharmaceutical substance, the hydrophobic particles in the dispersion come progressively closer together and ultimately form a water-impenetrable hydrophobic network. Thus a situation is reached which is analogous to the aforedescribed situation that occurs when particles of pharmaceutical substance are adhered to the surfaces of carrier particles.

Naturally, it is desirable to embody as much pharmaceutical substance as possible in dosage-unit form in order to obtain a good effect, even in the case of compositions in which the pharmaceutical composition is dispersed in a carrier. At the same time, it is also desirable to obtain a composition which will dissolve as quickly as possible, so as to achieve the effect intended quickly.

The present invention eliminates the aforesaid drawbacks to a large extent and provides a pharmaceutical composition which consists of finely-divided, particulate pharmaceutical substance in combination with a water-soluble carrier and which exhibits a rapid release rate of pharmaceutical substance even when the composition contains large quantities of said substance.

The invention thus relates to a pharmaceutical composition which enables rapid release of the pharmaceutical substance contained therein and which contains at least one finely-divided, hydrophobic pharmaceutical substance together with a water-soluble carrier, and is characterized in that it includes at least one surfactant in intimate mixture with the pharmaceutical substance. The surfactant is preferably present in an amount of

0.5-5 percent by weight, and then preferably in an amount of 0.5-3 percent by weight of the total weight of the composition.

Figures 1 and 2 of the accompanying drawings show the results of investigations relating to the solubility properties of pharmaceutical compositions prepared in accordance with a first embodiment of the invention. Figures 3 and 4 illustrate the results of investigations relating to the solubility properties of pharmaceutical compositions prepared in accordance with a second embodiment of the invention.

Surfactants have been used previously to some extent in connection with pharmaceutical preparations. For instance, surfactants have often been added to the solvent, with the purpose of assisting dissolution of tablets. Because the surfactant lowers surface tension, the tablet is wetted more readily and the liquid will penetrate the tablet more easily, so as to increase the area of surface contact between liquid and solid phase. This increases the speed at which dissolution takes place. For example, it is found that an addition of 0.01 percent by weight Tween ^{R}80 (polyethylene oxide (20) sorbitan monooleate) to an aqueous phase will provide the same surface-tension conditions as those conditions which are considered to exist in gastric juices.

Surfactants have also been used to promote the dissolution of pharmaceutical substances in micronized form. Such substances often form agglomerates, and consequently the surface-area available to the solvent becomes smaller, therewith resulting in a slower dissolution rate. The incorporation of a surfactant in the pharmaceutical preparation can result in improved wetting

and therewith a faster dissolution rate.

Surfactants have also been used widely to promote the solubilization of not-readily dissolved lipophilic substances. When a surfactant is added to water in sufficient quantities, micelles are formed by the agglomeration of the surfactant molecules. The lipophilic hydrocarbon parts of the molecules in the micelles face inwards towards the interior of the micelles, whereas the hydrophilic parts face outwards towards the water phase. The interior of the micelles can therefore be considered to be an organic phase which is capable of acting as an organic solvent. Substances which are not-readily dissolved in water can then be dissolved in this organic phase and the "water solubility" of the not-readily dissolved substances can often be enhanced considerably through this solubilization.

The present invention employs a surfactant in a manner which is different in principle to the manner previously used. According to the invention, the surfactant is used together with a mixture of a water-soluble carrier and a finely-divided, hydrophobic pharmaceutical substance, and enables larger quantities of pharmaceutical substance to be combined with the carrier while still achieving rapid dissolution of the pharmaceutical substance. The addition of surfactant has no appreciable effect on the dissolution rate of an ordered mixture of low surface-area ratio, e.g. a surface-area ratio of 0.1. On the other hand, a much faster dissolution rate is attained when a surfactant is added to an ordered mixture of high surface-area ratio, e.g. 0.7. The pharmaceutical substance contained in this ordered mixture will normally dissolve very slowly if no surfactant is added. This improvement is quite unexpected.

The surfactant may be of an anionic, a cationic or a non-ionic type, although the anionic and non-ionic surfactants are preferred. In fact, the surfactant need only fullfil the requirement of being pharmaceutically acceptable and thus shall not cause undesirble side-effects in the part of the patient. Neither shall the surfactant be capable of reacting unfavourably with the pharmaceutical substance, carrier or other material present in the composition. Examples of suitable anionic surfactants are sulphuric-acid esters, such as sulphated monoglycerides and alkylsulphates, and then sodium lauryl sulphate in particular, substituted alkyl amides, such as sarcosinates, and hemi-esters, such as sulphur-succinates. Non-ionic surfactants may consist in poly-alkoxy ethers, such as polyoxyethylene-polyoxypropylene block polymers, polyalkoxy esters, such as polyoxy-ethylene fatty acid esters and polyoxyethylene-oxide sorbitanic acid esters, and then Tween ^{R}80 (polyoxy ethylene oxide sorbitan monoleate) for instance, and fatty acid esters of multi-valent alcohols, such as glyceryl esters and sorbitan esters. Other surfactants can be used, as will be understood by the person skilled in this field.

The active pharmaceutical substance or substances present in the composition will normally have a particle size of at most about 10 microns, and then preferably at most about 6 microns.

As before mentioned, in a first embodiment of the invention the composition exists in the form of water-soluble carrier particles to which the pharmaceutical substance adheres, and the surfactant is finely-divided and in intimate mixture. The carrier will normally have a

particle size of 50-1000 microns, and then preferably 100-500 microns. Although it is possible to use particle sizes which lie outside the limits of the widest range, difficulties are experienced in practice when formulating pharmaceutical preparations from particles of such sizes.

The carrier material used may comprise any substance which is pharmaceutically acceptable, is highly soluble in water and can be formed into the desired particles. Several such materials are known to those skilled in this field and examples of such materials include carbohydrates, such as mannitol or lactose, or pharmaceutically acceptable inorganic salts, such as sodium chloride. In one expedient variant, the carrier material consists of a fragmentizing material. By fragmentizing material is meant a material which is crushed readily, or readily broken-up, when a pharmaceutical composition is compacted into tablets, so as to expose further surfaces. Carbohydrates, such as the above-mentioned mannitol and lactose, have been found particularly suitable in this respect. When the pharmaceutical preparation includes a lubricant, it has been found necessary to use a fragmentizing carrier material.

In the case of one suitable variant, the carrier particles also contain a pharmaceutical disintegrant or explosive agent. This agent assists in the rapid disintegration of the carrier particles and the rapid dissolution of the particles upon contact with water,so that the fine particles of pharmaceutical substance are released rapidly. The carrier particles can contain up to 25 percent by weight disintegrant and then suitably up to 10 percent by weight. Contents beneath 1 percent by weight are found to give a much too poor effect. An

optimal content-range would seem to be from about 5 to 10 percent by weight.

The pharmaceutical disintegrant may comprise any substance which is known for this purpose to those skilled in this art. Paricularly effective agents in this respect are those which swell drastically in water, through hydratization, and thus exhibit an increase in volume of up to 20-10 times their dry volume. Examples of such agents are cellulose and starch derivatives in the form of water-insoluble, cross-linked polymers which swell markedly in water. Derivatives of polyvinylpyrrolidone are other examples of such agents. One particularly suitable disintegrant for use in accordance with the present invention is a modified cellulose gum which is highly swellable in water and which is retailed under the trade name Ac-Di-Sol ^{R} by FMC Corporation, USA. Other types of disingregant can also be used. The disintegrant can be embodied in the carrier particles in various ways, all of which are known to the skilled person.

As before mentioned, in the case of the first embodiment of the present invention, the pharmaceutical substance and the surfactant, both in finely-divided form, exist in an intimate mixture adhering to the surfaces of the carrier particles. This can be achieved in several ways, for example by dry-mixing the pharmaceutical substance, the surfactant and carrier particles over a sufficiently long period of time. This period of time can vary and when mixing the components under laboratory conditions is from 10 to 100 hours, depending on the particular materials used and the method of mixing employed in detail. When mixing the components on an industrial scale, the requisite mixing time will be much shorter,

and is normally in the order of 10-60 minutes. An appropriate mixing period can be ascertained readily by one skilled in this art, on the basis of simple routine experiments.

The three components can be mixed together initially, or alternatively a premix can be prepared from two of the components and the third component admixed with the premix at a later stage. It is often found expedient to first mix the pharmaceutical substance with the carrier particles and then add the surfactant to the resultant premix and mixing the surfactant thoroughly therewith.

The value obtained with respect to the surface-area ratio R_s is significant with regard to the quantity of pharmaceutical substance which shall adhere to the surfaces of the carrier particles. In the case of one composition prepared in accordance with the present invention, the pharmaceutical substance will preferably be present in an amount which results in a surface-area ratio of at least 0.3 and then preferably at least about 0.7. The addition of a surfactant will not improve the rate of dissolution at lower surface-area ratio values and it is not until surface-area ratios of the higher values are reached that the advantages afforded by the present invention over the present standpoint of techniques actually become apparent. The surface-area ratio, however, should not exceed 1.0 to any appreciable extent.

A pharmaceutical composition prepared in accordance with the invention may have one or several mutually different pharmaceutical substances adhered to the surfaces of the carrier particles. Furthermore, one or more mutually different surfactants can be used in combination with

the pharmaceutical substance or substances.

The pharmaceutical compositions produced in accordance with the first embodiment of the invention may be included in different types of pharmaceutical preparations. The preparations will preferably be intended for enteral administration, primarily for oral administration. The preparations are, for instance, in tablet, capsule, powder or granule form, or in the form of suppositories for rectal administration. Pharmaceutical compositions prepared in accordance with the invention may also be used in preparations for external use, such as ointments or creams. Irrespective of the method of administration chosen, it is important that the preparation is essentially free from water, since the presence of water would result in premature dissolution of the pharmaceutical substance.

The pharmaceutical preparations can be formulated by combining the inventive pharmaceutical compositions with the conventional pharmaceutical additives and excipients normally used in the desired forms of the preparations, with the aid of known methods herefor. Such additions may comprise, for instance, additional carriers, preservatives, lubricants, glidants, disintegrants, flavorants, dyestuffs and like substances, and are well known to the person skilled in this art.

In the case of a second embodiment of the invention, the hydrophobic pharmaceutical substance and the surfactant are present in a finely-dispersed form in the water-soluble carrier. The pharmaceutical substance and the carrier are normally so adapted to one another that the pharmaceutical substance will dissolve in the carrier at elevated temperatures but will not readily dissolve

therein at lower temperatures, normally room temperature, such that the fine dispersion is obtained by precipitation of the pharmaceutical substance as the solution cools. The conditions which prevail during cooling of the solution can be adjusted in a manner to obtain a particle-size of appropriate fineness.

It is also conceivable for the pharmaceutical substance to be soluble in the water-soluble carrier at room temperature. In the case of the preferred embodiment, in which the carrier is solid at room temperature, there is obtained a solid solution of pharmaceutical substance in the carrier. This can be said to constitute the border case of a fine-dispersement of pharmaceutical substance in the carrier, and is also included in the invention.

According to the invention, a pharmaceutical composition prepared in accordance with this embodiment shall also contain at least one surfactant in finely-dispersed form and in intimate mixture with the pharmaceutical substance. This can be achieved by mixing the surfactant together with the pharmaceutical substance in the liquid carrier at elevated temperature. In this case, the surfactant, similar to the pharmaceutical substance, is dissolved in the hot carrier and precipitates in a finely dispersed form as the solution cools, or the surfactant may, alternatively, be not-readily dissolvable in the carrier and is in a sufficiently finely-divided form at the stage of being mixed with the carrier. It is also conceivable for the surfactant to remain dissolved in the carrier, even at room temperature, without preventing the surfactant from exerting the desired effect when the composition is dissolved in water in use.

Similar to the first embodiment, the surfactant may be present in the pharmaceutical composition in an amount corresponding to 0.5-5 percent by weight, preferably 0.5-3 percent by weight of the total composition.

The carrier material used in the second embodiment shall consist of a water-soluble material in which the pharmaceutical substance can be dispersed in a finely-divided state. In the preferred case, the pharmaceutical substance is soluble in the carrier at elevated temperature, but precipitates in a finely-divided form when the solution cools. It is preferred that the carrier is solid at room temperature although liquid at said temperature when the pharmaceutical substance is dissolved, since this facilitates handling of the pharmaceutical composition in its finished form.

It is also conceivable for the pharmaceutical substance to be not-readily soluble in the carrier at elevated temperature. In these cases, the finely-divided pharmaceutical substance is finely-dispersed mechanically in the liquid carrier at the elevated temperature, whereafter the resultant mixture is allowed to cool while maintaining the dispersion until the carrier has solidified or has become sufficiently viscous for the dispersion to be maintained over an unlimited period of time.

The surfactant will also preferably exhibit similar dissolution and dispersion properties as the pharmaceutical substance or substances used, but need not perform in precisely the same manner as the substance or substances. The important criterion is that the final product includes an intimate mixture of pharmaceutical substance and surfactant in finely-divided form dispersed in the water-soluble carrier. Provided that this

result is achieved, it is irrelevant if one or both of the components have been dissolved in the carrier or mechanically dispersed therein.

Several carrier materials which fullfil the requirements placed thereon are known to the person skilled in this art, and polyethylene glycol of varying molecular weights can be mentioned as an example of suitable carrier material. Polyethylene glycol having a molecular weight within the range of about 3000 to about 20000, and then particularly about 3000, has been found suitable because of its good dissolution properties in a molten state, while at the same time being solid and easily handled at room temperature. Examples of further carriers include xylitol and sorbitol.

The amount of pharmaceutical substance incorporated in the carrier can vary within wide limits, and is determined to a large extent by the solubility and dispersability of the substance in the carrier. It will be readily understood that the addition of surfactant in accordance with the invention affords the greatest advantages at high content values, at which the particles of the hydrophobic pharmaceutical substance would otherwise form a dense, hydrophobic network which prevents penetration of the water. The present invention affords practically no advantages at low contents, since the particles of pharmaceutical substance are then still spaced widely apart and are thus unable to prevent dissolution. For example, the pharmaceutical substance may be present in the carrier in an amount corresponding to from 5 to 50 percent by weight of the total pharmaceutical composition, and then preferably from 5 to 25 percent by weight, although these values are not critical.

Pharmaceutical compositions according to the second embodiment of the invention can be formulated to provide pharmaceutical preparations similar to the compositions according to the first embodiment. However, since the carrier in this case may be more or less semi-liquid, certain modifications must be made, as will be evident to the person skilled in this art. For instance, tablets, powder and granulates may then be of less interest, whereas liquid-filled capsules can represent a suitable form of dosage.

The active pharmaceutical substances capable of being included in the inventive pharmaceutical compositions can vary very widely. Any pharmaceutical substance which, together with a surfactant, can be brought to a sufficiently small particle size and be caused to adhere to the surfaces of water-soluble carrier particles, or can be dispersed in a water-soluble carrier, can be used within the scope of the present invention. The advantages afforded by the present invention are obtained primarily when using hydrophobic pharmaceutical substances which are not-readily dissolved in water, although the degree of solubility in water can vary with the type of substance used, and the intention is not that the solubility of the active pharmaceutical substance or substances shall constitute a limitation of the invention. It is simple for one skilled in this art to establish by routine experiment whether or not a pharmaceutical substance can be used in a pharmaceutical composition according to the invention.

Benzodiazepines, ergotamine tartrate, isosorbide dinitrate and griseofulvin are examples of different types of active substance which can be used in conjunction

with the present invention. This recitation of suitable active substances is not in any way exhaustive, however.

The invention will be illustrated more clearly with the aid of the following non-limitive working examples and with reference to the accompanying drawings.

Example 1

This example illustrates the effect of the addition of a surfactant on the dissolution rate of an ordered mixture having a low surface-area ratio.

Dry mannitol having a particle size of 250-450 microns was mixed with micronized oxazepam of such fineness that the external specific surface-area, measured with a permeametric surface-area method, was not less than 20000 cm^2/g. A surface-area ratio of 0.1 was obtained, which corresponds to an oxazepam-addition of 0.26 percent by weight.The mixing time was about 50 hours. The resultant ordered mixture was then divided into two parts.

2.7 percent by weight sodium lauryl sulphate having a particle size of beneath 10 microns was added to the first part and the components were mixed together for 100 minutes. The dissolution rate of each of the mixtures was then determined in accordance with U.S.P. XXI, pages 1243-1244, the paddle method, at room temperature and a stirring speed of 100 rpm. Results are shown in Figure 1.

It will be seen from the curves shown in Figure 1 that an addition of a surfactant to an ordered pharmaceutical mixture of low surface-area ratio does not influence the dissolution rate to any great extent.

Example 2

This example illustrates the influence of a surfactant on the dissolution rate of an ordered mixture that has a high surface-area ratio.

Dry mannitol having a particle of 250-450 microns was mixed dry with micronized oxazepam of such fineness that the external specific surface-area, measured with permeametric surface-area method, was not less than 20000 cm^2/g. A surface-area ratio of 0.7 was obtained, which corresponded to an oxazepam-addition of 1.8 percent by weight. The mixing time was about 50 hours. The resultant ordered mixture was then divided into three parts.

Two of these parts were admixed respectively with 1.35 and 2-7 percent by weight sodium lauryl sulphate having a particle size beneath 10 microns, and each of said parts was mixed for 100 minutes. The dissolution rate of the three different mixtures was then determined directly in accordance with U.S.P. XXI, pages 1243-1244, the paddle method, at room temperature and a stirring speed of 100 rpm. Results are shown in Figure 2.

It will be evident from the curves shown in Figure 2 that an addition of sodium lauryl sulphate improves the dissolution rate at high surface-area ratio values, and that the higher addition results in greater improvement. Consequently, when adding a surfactant to an ordered pharmaceutical mixture it is possible to include a larger quantity of pharmaceutical substance than was previously possible with known techniques, while nevertheless obtaining a high dissolution rate.

Example 3

This example illustrates the use of a surfactant together with a finely-dispersed pharmaceutical substance in a water-soluble carrier.

10 percent by weight griseofulvin was dissolved in warm polyethylene glycole 3000 and the solution was divided into two batches. 1 percent by weight sodium lauryl sulphate was dissolved in one of the batches, whereafter the two batches were allowed to cool to room temperature. The griseofulvin precipitated in a finely-dispersed form having a particle size of about 3 microns.

The dissolution rate of the two batches having a particle size of 300-500 microns was then determined in accordance with U.S.P. XXI, pages 1243-1244, the paddle method, in distilled water with various additives. These additives comprised sodium lauryl sulphate in quantities of 0.1, 0.01 and 0.001 percent by weight, Tween 80 ^{R} (polyethyleneoxy-disorbitane monooleate) in quantities of 0.1 and 0.001 percent by weight, and Tween 80 ^{R} in the same quantities but with a further addition of 0.9 percent by weight NaCl. The results of the dissolution tests carried out are set forth in Figures 3 and 4.

It will clearly be seen from Figure 3 that the surfactant content of the dissolution water is significant to the rate of dissolution when the composition itself contains no surfactant. Thus, at low surfactant contents of 0.001 percent by weight essentially the same rate of dissolution is obtained as that of pure water, and it is found that hardly half of the composition has dissolved after a lapse of 20 minutes. As expected, the dissolution rate increases with higher contents in the water solvent, although it will be noted that even when the

amount of sodium lauryl sulphate present in the water it as high as 0.1 percent, it still takes about 10 minutes for all the composition to pass into solution. This is considered to be a good result when practising prior art techniques.

Figure 4 shows clearly that, quite unexpectedly, with an addition of 1 percent sodium lauryl sulphate in finely dispersed form in mixture with the pharmaceutical substance in the carrier, the dissolution rate is essentially independent of whether or not the water solvent contains an additional surfactant. The dissolution rate increases so markedly that about 90 percent of the composition has passed into solution after a time lapse of only about two minutes, even when no surfactant whatsoever is present in the water solvent. This constitutes an important and unexpected improvement with respect to prior art techniques.

The present invention, in its various embodiments, enables the manufacture of pharmaceutical compositions which contain higher quantities of active pharmaceutical substance than was earlier considered possible in practice, while nevertheless exhibiting an equally as rapid or even more rapid release of the pharmaceutical substance when dissolved in water, and thereby a more rapid therapeutic effect. This constitutes a considerable and unexpected step forward in the field of pharmaceutical formulation.

In the aforegoing examples, the invention has been described primarily with reference to the use of specific combinations of pharmaceutical substance, carrier and surfactant. It will be apparent to those skilled in this art, however, that the invention is not limited to

such combinations and that other combinations will also afford the advantages before mentioned and that variations in such conceivable combinations are only limited by the following claims.

CLAIMS

1. A pharmaceutical composition for rapid release of pharmaceutical substance and containing at least one finely-divided, hydrophobic pharmaceutical substance together with a water-soluble carrier, characterized in that the composition also contains at least one surfactant in intimate mixture with the pharmaceutical substance.

2. A composition according to Claim 1, characterized in that the surfactant is present in an amount of 0.5-5 percent by weight, and then preferably 0.5-3 percent by weight of the composition.

3. A composition according to Claim 1 or 2, characterized in that the pharmaceutical substance has an average particle size of at most about 10 microns and then preferably at most about 6 microns.

4. A composition according to any one of Claims 1-3, characterized in that the carrier consists of water-soluble particles to which the pharmaceutical substance and the surfactant in finely-divided form adhere.

5. A composition according to Claim 4, characterized in that the carrier has an average particle size of 50-1000 microns, and then preferably 100-500 microns.

6. A composition according to Claim 5 or 5, characterized in that the pharmaceutical substance adhering to the carrier particles is present in an amount which gives a surface-area ratio R_s of at least 0.3, and then preferably at least 0.7.

7. A composition according to any one of Claims 4-6, characterized in that a pharmaceutical disintegrant is embodied in the carrier particles.

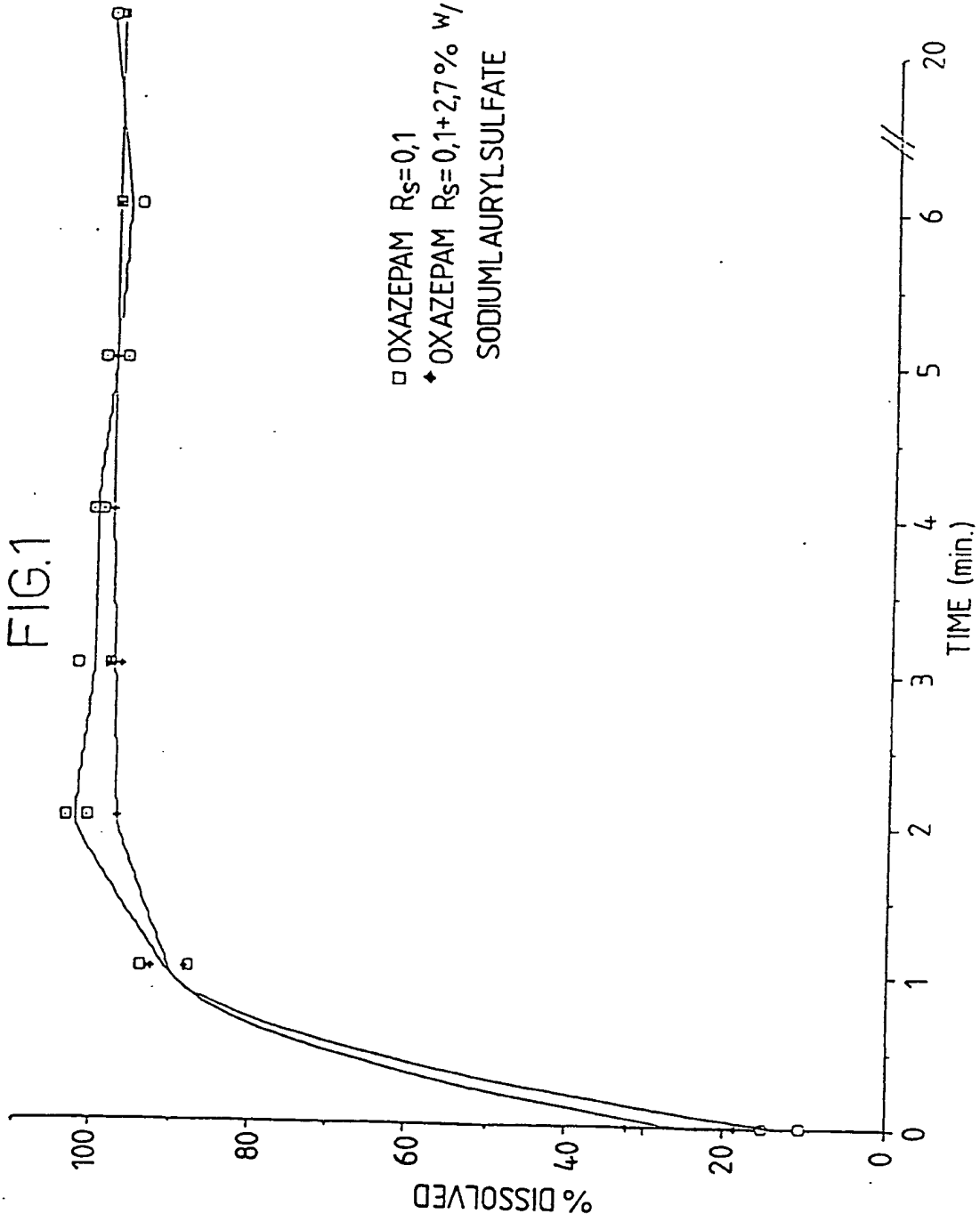
8. A composition according to any one of Claims 1-3, characterized in that the pharmaceutical substance is present in the carrier in a finely-dispersed or dissolved state.

9. A composition according to Claim 8, characterized in that the carrier consists of a material in which the pharmaceutical substance will dissolve at elevated temperature but is not-readily dissolved at room temperature.

10. A composition according to Claim 9, characterized in that the carrier consists of a material which is liquid at the temperature at which the pharmaceutical substance is soluble but is solid at room temperature.

11. A pharmaceutical preparation, characterized in that it contains at least one pharmaceutical composition prepared in accordance with any one of Claims 1-10.

FIG.1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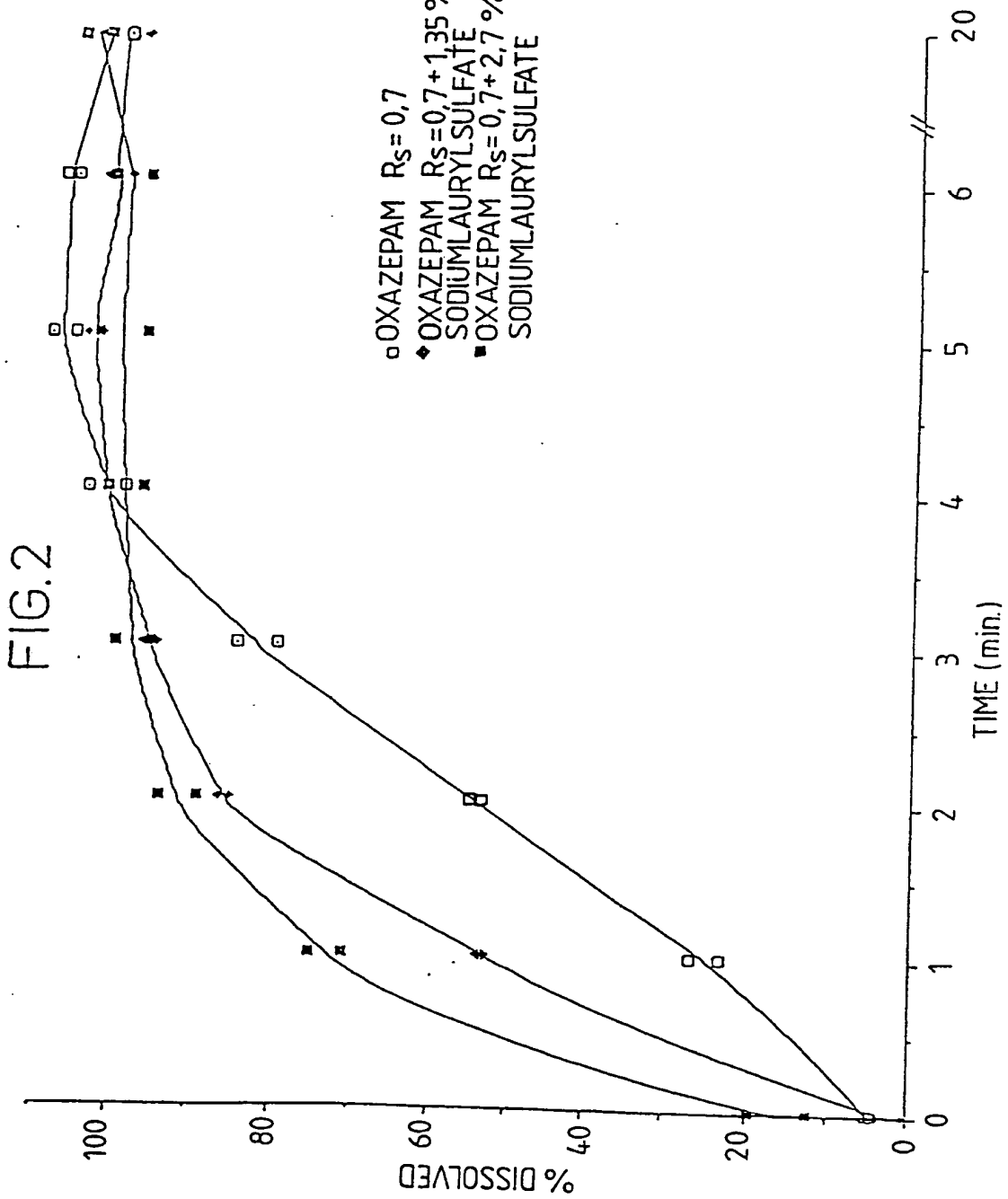
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FIG.2

FIG.3

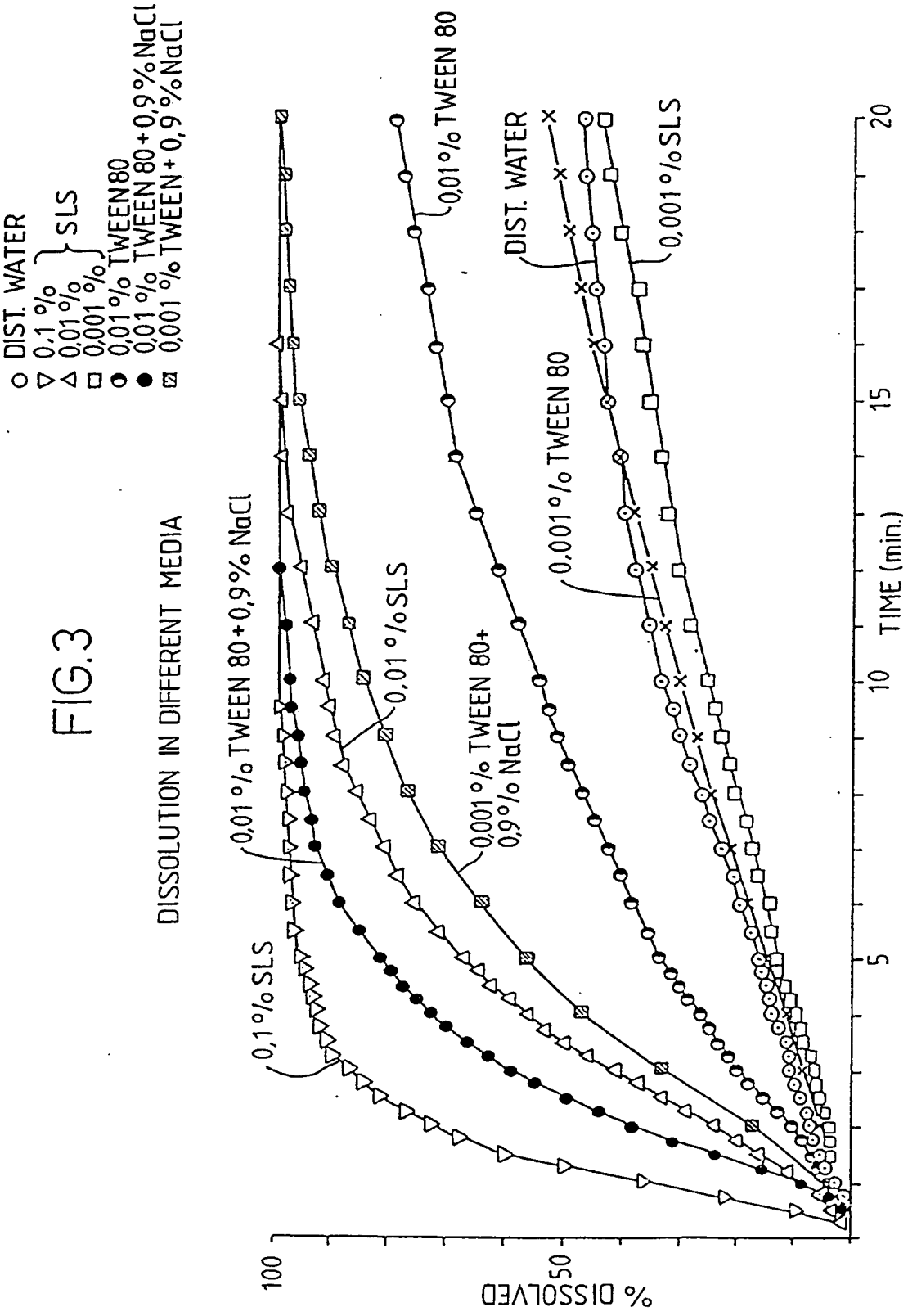
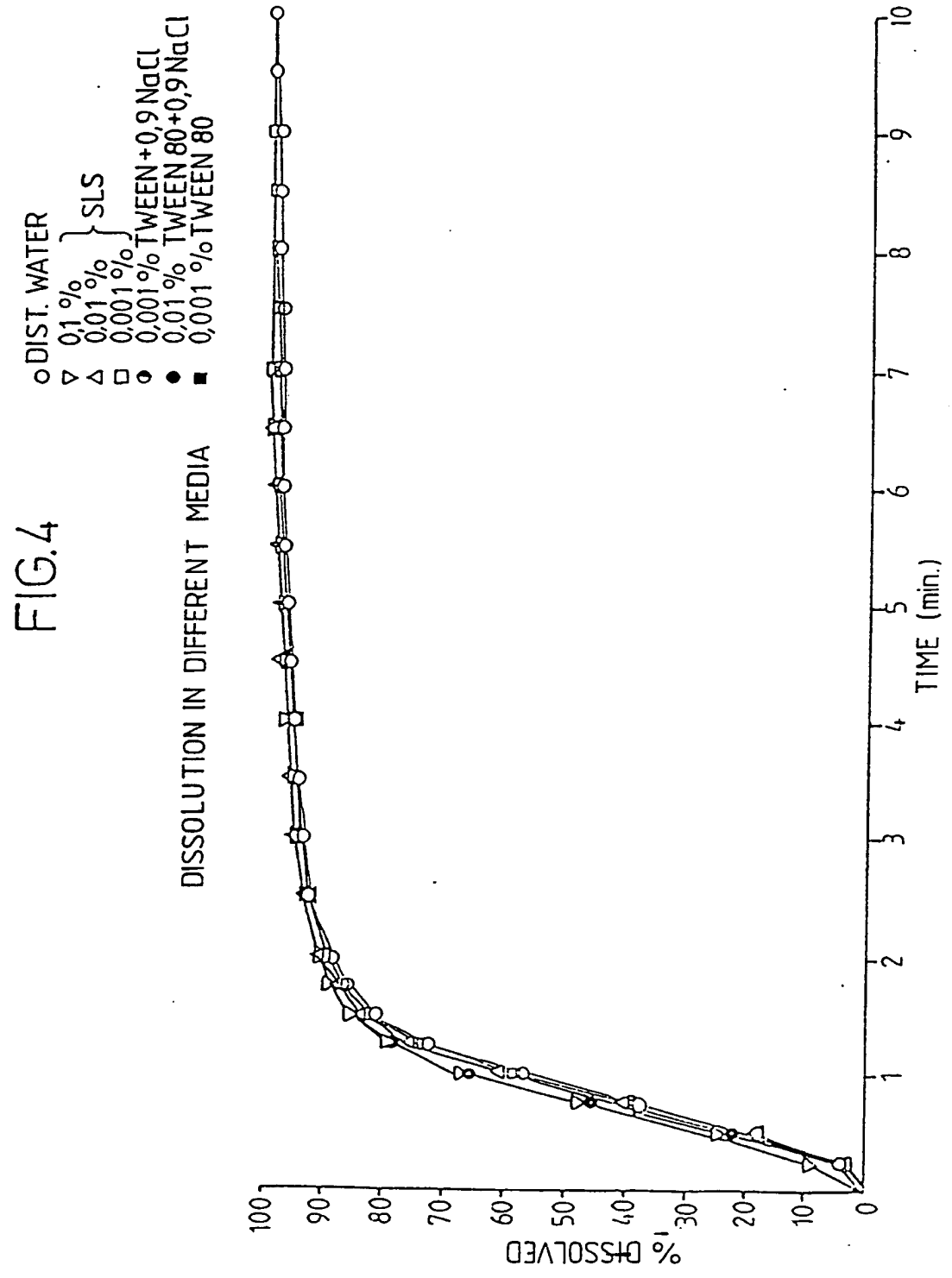

DISSOLUTION IN DIFFERENT MEDIA
DIST. WATER
0,1 %
0,01 %
0,001 %
SLS
0,01 % TWEEN 80
0,01 % TWEEN 80+0,9 % NaCl
0,001 % TWEEN+0,9 % NaCl
0,1 % SLS
0,01 % TWEEN 80+0,9 % NaCl
0,01 % SLS
0,001 % TWEEN 80 0,9 % NaCl
0,01 % TWEEN 80
DIST. WATER
0,001 % TWEEN 80
0,001 % SLS
% DISSOLVED
100
50
5
10
15
20
TIME (min.)

FIG.4


DISSOLUTION IN DIFFERENT MEDIA
o DIST. WATER
▽ 0,1 %
△ 0,01 %
□ 0,001 % } SLS
○ 0,001 % TWEEN+0,9 NaCl
● 0,01 % TWEEN 80+0,9 NaCl
■ 0,001 % TWEEN 80
% DISSOLVED
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
TIME (min.)

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE89/00599

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC [5]

A 61 K 9/18, 9/14, 47/20

II. FIELD SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

SE, NO, DI, FI classes as above.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A1, 0 012 523 (AMERICAN HOME PRODUCTS CORPORATION) 25 June 1980 See the whole document	1-11
X	Powder technology, 1984, Iinoya et al, "Ordered Mixes of Hydrophobic Drugs and a Directly Compressible Excipient-Dissolution and Uniformity Properties", pages 734-741	1-11
Y		1-11
Y	Pharmaceutisch Weekblad Scientific Edition, Vol 6, 1984, E.J. de Jong and C.J. de Blaey, "A new approach of ordered mixing applied to digitoxin tablets" pages 16-17	1-11
X	WO, A1, 87/00428 (SETH, PYARE) 29 January 1987 See claims 1-9,13-14	1

.../...

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1989-12-29	1990 -01- 12
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Mikael G:son Bergstrand

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS C NSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US, A, 4 744 976 (WALLACE C. SNIPES ET AL) 17 May 1988 See especially the abstract	1-2

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 89/00599

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A1- 0012523	25/06/80	US-A-	4344934	17/08/82
		AT-E-	5852	15/02/84
WO-A1- 87/00428	29/01/87	EP-A-	0232254	19/08/87
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		EP-A-	0190255	13/08/86
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		US-A-	4774074	27/09/88
		CA-A-	1246448	13/12/88
		US-A-	4806337	21/02/89